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Rescue Therapy for Refractory Vasospasm after Subarachnoid Hemorrhage

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Abstract

Vasospasm and delayed cerebral ischemia remain to be the common causes of increased morbidity and mortality after aneurysmal subarachnoid hemorrhage. The majority of clinical vasospasm responds to hemodynamic augmentation and direct vascular intervention; however, a percentage of patients continue to have symptoms and neurological decline. Despite suboptimal evidence, clinicians have several options in treating refractory vasospasm in aneurysmal subarachnoid hemorrhage (aSAH), including cerebral blood flow enhancement, intra-arterial manipulations, and intra-arterial and intrathecal infusions. This review addresses standard treatments as well as emerging novel therapies aimed at improving cerebral perfusion and ameliorating the neurologic deterioration associated with vasospasm and delayed cerebral ischemia.

Keywords

Aneurysmal subarachnoid hemorrhage; Vasospasm; Delayed cerebral ischemia; Refractory vasospasm; Hemodynamic augmentation; Intraluminal balloon angioplasty

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) may produce devastating morbidity through its most serious complication— vasospasm. aSAH is estimated to affect 30,000 patients annually in the USA [1]. Gradual arterial narrowing occurs in 70 % of patients over a 2-week period after aneurysm rupture [2, 3]. Approximately 30 % will develop persistent neurological deficits characteristic of delayed cerebral ischemia. Vasospasm and delayed cerebral ischemia are treated by a variety of medical and interventional methods, including hemodynamic augmentation and direct vascular intervention.

A small subset of patients has vasospasm that is refractory to standard treatment. These patients are at particularly high risk for increased morbidity and mortality. This review will

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

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address standard treatments such as induced hypertension as well as emerging novel therapies aimed at ameliorating the neurologic deterioration associated with vasospasm.

Epidemiology

Vasospasm

Vasospasm refers to the narrowing of cerebral arteries detected by angiography or sonography [4•, 5•]. Complex pathological changes occur in the cerebral circulation, leading to thickened walls from subendothelial fibrosis [6] and impaired vasodilation [7]. Arterial narrowing starts 3–5 days after SAH, with maximal narrowing between 5 and 14 days and gradually resolves between 2 and 4 weeks [3]. When combined with impaired autoregulation and intravascular volume depletion, cerebral blood flow is reduced. If severe or prolonged, ischemia and infarction may follow [8].

Delayed Cerebral Ischemia

Delayed cerebral ischemia (DCI) is defined as the presence of focal neurological deficit or a decrease in the Glasgow Coma Scale of at least two points. Deficits should last longer than one hour, should be absent immediately after aneurysm occlusion, and should not be attributable to other causes [3,8]. It occurs in approximately 30 % of aneurysmal subarachnoid hemorrhage 3–14 days after rupture [3]. DCI has historically been thought to be directly related to vasospasm, but animal models and postmortem evaluation suggest that it is likely multifactorial. Indeed, therapeutic trials targeting the reversal of proximal vasoconstriction improved angiographic vasospasm but did not improve functional outcomes, suggesting that the causation of vasospasm and DCI may not be as unequivocal [9, 10•]. Inflammatory cells within the intima of the blood vessels have been observed, causing endothelial dysfunction and necrosis [6]. Microglial activation in early subarachnoid hemorrhage correlates with the later development of vasospasm in murine models [11]; further histological studies in humans are needed [12•]. Inflammatory cascades [12•, 13], oxidative stress and cortical spreading depression (a depolarization wave in the cerebral gray matter that propagates across the brain) [8, 14], and microthrombosis [8, 12•, 13, 15, 16] all likely contribute to the development of DCI. A more complete understanding of their role in vasospasm and DCI will be an important contribution to the direction of future clinical trials [17].

Diagnosis

Clinical Exam

The diagnosis of delayed cerebral ischemia is a clinical diagnosis. Symptoms are often subacute, can fluctuate [18], and can be subtle, non-focal, or absent in patients with a poor neurological exam after the initial hemorrhage or in those receiving sedating medications [19]. Thus, ultrasonography and radiography investigations are implemented to supplement the neurological exam.

Imaging

Transcranial Doppler (TCD) ultrasonography remains to be the primary noninvasive method for detection of vasospasm [20]. By measuring elevations of mean cerebral blood flow velocities [21], it is almost as sensitive as conventional angiogram in detecting vasospasm; however, utility is limited by poor insonation windows in a portion of patients [22], failure to correct for external alterations of cerebral blood flow (such as augmentation of blood pressure) [23], and operator interpretation differences [20].

Cerebral digital subtraction angiography (DSA) remains to be the gold standard for the diagnosis of radiographic vasospasm via vessel caliber and transit time calculations [20]. Disadvantages include radiation and iodine contrast exposure, risk of iatrogenic stroke or catheter-induced vascular injury relatively high cost, and requirement of an experienced operator [20, 24].

Other imaging modalities have gained favor in recent years, including computer tomography perfusion, Xenon-enhanced computed tomography, diffusion-weighted magnetic resonance imaging, and single-photon emission computed tomography [20]. These methods measure regional perfusion as opposed to vessel diameter and flow velocities. Continuous electroencephalogram has also gained new application in the early detection of DCI [25,26]. Cortical spreading depression, a depolarizing wave that originates in the gray matter and depresses evoked and spontaneous brain activity [8, 14], has been linked with various etiologies of brain ischemia [27•] and changes in CBF manifested as alterations to background EEG patterns. In one study, authors found that certain patterns of early EEG alterations (day 1 after SAH) predicted later vasospasm [27•, 28].

Medical Therapies

Myriad medical options are deployed to prevent vasospasm, including calcium channel blockers, statins, endothelial receptor antagonists, and others [29]. Comparatively, fewer investigations focus on reversing or minimizing the effects of vasospasm. The literature that does exist almost universally comes from small, uncontrolled trials that lacked randomization or a control group. Definitive therapeutic recommendations are difficult to endorse without higher levels of evidence. Nevertheless, we will focus on therapies implemented after the detection of vasospasm and/or DCI (Table 1).

Hemodynamic Augmentation

The so-called “triple-H therapy” (hypervolemia, hypertension, and hemodilution) remains to be a key facet of the medical management of clinical and radiographic vasospasm [30]. This technique augments cerebral blood flow by expanding intravascular blood volume, reducing blood viscosity, and supporting cerebral blood flow to hypoperfused areas [31]. Augmenting cerebral perfusion improves symptoms in nearly 75 % of patients [32]. Complications of this strategy include pulmonary edema, hypoxemia, and anasarca, which limit the utility of volume expansion [32-34]. Literature does not support the institution of the triple-H therapy prior to symptomatic vasospasm [31, 35]. Studies evaluating prophylactic hypervolemia demonstrated no reduction in the incidence of vasospasm and delayed cerebral ischemia and were accompanied by more medical complications and increased cost of care [29-31,36].

Additionally, circulating blood volume correlates poorly to fluid balance [37] and sustained intravascular volume expansion is difficult to maintain [38, 39]. The benefit observed with the triple-H strategy likely derives from increased mean arterial pressure. There is a reported association between improved cerebral blood flow and neurological outcomes in patients with DCI who underwent induced hypertension [40-42]. The most recent American Heart Association/American Stroke Association guidelines (2012) recommend targeted euvolemia combined with induced hypertension for the clinical symptoms of DCI as tolerated by cardiac output [43].

Induced hypertension has been associated with reversal of neurological deficits in approximately two thirds of patients with DCI based on observational studies [30, 40, 44]. Investigators have primarily focused on dopamine to augment blood pressure in clinical studies [41, 42]. Clinicians frequently use phenylephrine and norepinephrine and, less readily, dopamine [45] likely due to the dose-independent variations in cardiac output and cerebral blood flow from dopamine [41] as well as concern for increased intracranial pressure [44]. Prospective, open-label trials indicate that phenylephrine is safe and efficacious as a first-line pressor with preserved left ventricular function [46, 47].

SAH causes disruptions to autoregulation [48]. Increases in cardiac output might independently affect cerebral blood flow in periods of ischemia [44, 49], regardless of the absolute differences in mean arterial pressure. Levy et al. described 23 patients with symptomatic vasospasm refractory to volume resuscitation who had improved cardiac output, unchanged mean arterial pressure (MAP) measurements, and improved neurological deficits with the introduction of dobutamine [50]. However, in a small recent study by Rondeau et al. that compared the augmentation of cardiac index with dobutamine and targeted mean arterial pressure elevation with norepinephrine, the development of vasospasm or delayed cerebral ischemia was unchanged in both groups [51•]. Further studies are needed.

Milrinone has also gained favor for inotropic augmentation, partially because of its vasodilatory effects on vessels due to its effects as a phosphodiesterase III inhibitor that interacts with the cyclic adenosine monophosphate (cAMP) pathways [52•]. It was first evaluated as an intra-arterial infusion in 2001 [53] and subsequently confirmed by several authors to reduce arterial spasm [54-56]. Lannes et al. presented a large case series of patients treated with a homeostatic protocol for symptomatic vasospasm which included an infusion of milrinone [52•]. The Montreal Neurological Hospital protocol was applied to 88 patients with symptomatic vasospasm, which entailed a bolus of milrinone followed by a continuous infusion for a mean of 9.8 days while maintaining euvolemia. Only one patient in the cohort needed intra-arterial milrinone as a rescue therapy for unabated symptoms, while no one required angioplasty. Medical complications, including pulmonary edema, myocardial ischemia, severe hypotension, and arrhythmia, were minimal. Seventy-five percent had a good neurological outcome at 1 year as defined by a modified Rankin score of 2 or less [52•]. While milrinone might be a safe addition to the medical treatment of vasospasm, no stronger conclusions should be drawn until a prospective, controlled trial is performed [44, 49, 52•, 54-57]. Likewise, arginine vasopressin (AVP) may hold promise as a complementary second vasopressor agent in patients failing to meet goal MAP on a single

agent [58]. The addition of AVP to phenylephrine in a retrospective cohort of patients with symptomatic vasospasm seemed to be safe, and it reduced the doses of catecholamine needed to achieve target MAPs.

Vasorelaxation

Calcium Channel Blockers—While well established in vasospasm prophylaxis, calcium channel blockers also may play a role in treatment. At the bedside, some investigators advocate the use of intrathecal (IT) calcium channel blockers, specifically nicardipine and nimodipine, usually delivered via an extraventricular drain (EVD) [59, 60]. The literature comprises retrospective, mostly uncontrolled cohort studies. Investigators observed reduction in TCD velocities [61, 62] but no differences in 90-day outcomes between those treated with IT calcium channel blockers and historical controls [62].

Nitric Oxide—Agrawal and colleagues studied IT sodium nitroprusside administered through an Ommaya reservoir in an uncontrolled, open-label cohort study. They found that IT sodium nitroprusside lowered TCD velocities, and observed improvement in GCS after therapy [63]. IT sodium nitroprusside seems to decrease angiographic spasm as well [64]. Salunke and colleagues conducted an open-label study of enteral sildenafil (100–150 mg every 4 h) for refractory vasospasm, which was administered to 72 patients. Twelve of those patients had at least transient if not permanent reduction in TCD velocities [65].

Magnesium—A large, placebo-controlled study investigated the use of continuous magnesium infusion for 20 days initiated after aneurysm ruptured. There was no difference in outcome at 3 months; the authors did not report on differences in the detection of vasospasm [66]. Though mostly investigated as a prophylactic, IV magnesium boluses do not seem to impact TCD velocities in patients with active vasospasm [67].

Interventional Therapies

Medical Intra-arterial Therapies

Intra-arterial (IA) infusion of papaverine was an early strategy to achieve vasodilation and improved neurological deficits in refractory vasospasm [68]. The efficacy of IA papaverine is equivocal [69]. Some investigators have raised concerns for paradoxical vasospasm and increased ICP, limiting the clinical utility of IA papaverine [70, 71].

Bolus-dosed IA verapamil, in contrast, has gained popularity in use for symptomatic vasospasm [72]. Several retrospective studies suggest neurologic improvement after single-dose verapamil was delivered via an intra-arterial catheter into the affected vessels [72, 73]. Some evidence suggests that IA verapamil may not change the caliber of the arteries, suggesting that simple vasodilation might not be the primary driver of neurologic improvement [74]. In contrast, an IA nicardipine bolus does seem to reduce angiographic and TCD evidence of spasm after treatment [75–77]. A case report suggests that dantrolene delivered intra-arterially might also be helpful in severe cases [78]. Dantrolene has also been used intravenously for refractory vasospasm in a small case series [79].

Continuous IA infusions have also been investigated. Several case series of continuous IA nimodipine indicate that this might be a safe strategy for critically ill patients in the ICU [80, 81]. A small case series of patients who underwent continuous intra-arterial nimodipine in the ICU for 1–5 days had improvement in their angiographic signs of vasospasm, and 13 seemed to have good clinical outcomes (Glasgow Outcome Scale (GOS) of 4 or 5) [82•].

Mechanical IA Therapies

Angioplasty—Intraluminal balloon angioplasty was first reported 30 years ago and is possibly one of the best-documented therapies for refractory vasospasm in the literature [83]. A catheter introduces a balloon, which is inflated inside the lumen of the affected vessel. Investigators have routinely observed improvements both in vessel diameter and neurologic symptoms after treatment [84–88]. One randomized, controlled trial was conducted comparing early, prophylactic angioplasty to diagnostic angiogram alone [89]. In this trial, angioplasty was done prophylactically, less than 96 h after ictus and prior to evidence of delayed cerebral ischemia. Angiographers performed angioplasty to bilateral A₁, M₁, and P₁ segments unless technical constraints prevented them from doing so. Both groups received the prophylactic triple-H therapy as well. Either group could undergo rescue angioplasty for symptomatic DCI during the ensuing hospital course. Outcomes between the intervention and control groups were similar; however, fewer patients in the prophylactic angioplasty group needed subsequent rescue angioplasty. This study did not definitively prove the efficacy of angioplasty for refractory vasospasm but does suggest that the technique is likely a safe option for therapeutic intervention. Angioplasty does appear to improve diffusion/perfusion mismatch on MRI in spastic arteries [90]. The major complications associated with angioplasty include vascular injury or perforation, hemorrhage, and death.

Angioplasty may be combined with bolus dosing of IA therapy. There is evidence that IA Ca⁺ channel blockers and angioplasty might have similar effects on long-term outcomes [91], though these techniques have not been compared in a controlled fashion.

Aortic Obstruction

Novel approaches to improving cerebral perfusion in vasospasm include transient aortic obstruction. A balloon catheter is inserted into the femoral artery and inflated about and below the renal arteries in order to occlude the abdominal aorta lumen to 70 % of its diameter. Aortic obstruction has been shown to improve cerebral blood flow in experimental ischemic stroke patients. Lylyk and colleagues conducted an open-label study of aortic obstruction with a novel device in a small cohort of subjects ($n=24$) with refractory vasospasm [92]. All had improvement of TCD velocities, and 20 had improvement in their neurologic exams (quantified by NIH Stroke Scale scores).

Emerging Therapies

Hypothermia

While hypothermia has not yielded reliable clinical neuroprotection in stroke, traumatic brain injury, or status epilepticus, hypothermia might help arrest neuroinflammation

contributing to vasospasm. Seule et al. reported on 11 patients diagnosed with DCI treated with induced hypothermia, which leads to decreased mean middle cerebral velocities via TCD during the period of hypothermia [93•].

Anesthetics

Anesthetizing the stellate ganglion is thought to improve cerebral perfusion by decreasing cerebrovascular resistance. A recent case series described patients with DCI attributable to vasospasm that underwent stellate ganglion blockage. Injections were done bedside and confirmed when the patient developed an ipsilateral Horner's syndrome. Eleven of the 15 patients demonstrated improvement in their neurologic deficits, and all experienced decreases in TCD-measured arterial velocities [94•].

Immunomodulators

Immunosuppressants (steroids, cyclosporine, and nonsteroidal anti-inflammatory drugs) have been studied extensively in animals and humans as agents to prevent vasospasm [95]. Results have been mixed but can be summarized as disappointing. Due to burgeoning research of the role of inflammation and microvascular dysfunction in vasospasm and DCI, this will likely be an area of targeted therapies in the coming years.

Conclusion

Despite suboptimal evidence, clinicians have several options in treating refractory vasospasm in aSAH. Investigators are pushing the boundaries of care beyond conventional vasorelaxation techniques. It is likely that techniques aimed at improving cerebral perfusion and decreasing the inflammatory component of vasospasm will be figured prominently in the next generation of therapy for refractory vasospasm.

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Table 1

Therapeutic agents for the treatment of refractory vasospasm and levels of evidence. Quality of evidence assessed using the grade system

Agent	Site of administration	Mechanism	Quality evidence
Induced hypertension with pressors	IV	Increased mean arterial pressure±increased cardiac output	Level of evidence B
Intraluminal angioplasty	IA, local	Mechanical enlargement of arteries	Level of evidence B
Calcium channel blockers	IA with bolus dosing	Vascular relaxation±anti-inflammatory	Level of evidence C
Calcium channel blockers	IA with continuous infusion	Vascular relaxation±anti-inflammatory	Level of evidence C
Aortic obstruction	IA, remote	Mechanical augmentation of cerebral perfusion	Level of evidence C
Calcium channel blockers	IT	Vascular relaxation±anti-inflammatory	Level of evidence D
Nitrous oxide	IT	Vascular relaxation	Level of evidence D
Hypothermia	Systematic	Multiple	Level of evidence D
Stellate ganglion block	Nerve	Autonomic modulation	Level of evidence D

IV intravenous, *IT* intrathecal, *IA* intra-arterial